REMARKS

Claims 1-18 and 20-38 are pending in the instant application, and all of the pending claims are rejected. Upon entry of the instant amendment, claims 1-18, 20-24 and 28-42 will be pending.

As a preliminary matter, Applicants herein amend the paragraph including lines 7 to 28 on page 8 by changing the international patent application numbers to the corresponding international patent publication numbers. Clearly, no issue of new matter arises by way of this minor change.

Rejection under 35 U.S.C. §102

The Examiner rejects all of the pending claims as unpatentable under 35 U.S.C. §102.

1. Schnieke *et al., Science* 278:2130-2133 (1997)

The Examiner rejects claims 25-27 as anticipated by Schnieke *et al.* According to the Examiner, Schnieke *et al.* teach sheep embryos, sheep fetuses and live born sheep from transgenic methods. The Examiner does not believe that our arguments as filed distinguish the prior art animals from those presently claimed. Applicants previously explained unexpected results citing to the Declaration of Lawrence Smith and stating that the method of the claimed invention results in 40% of nuclear transfer embryos developing into offspring when a nucleus is transferred into a telophase II oocyte.

The Examiner makes the following points:

1. According to the Declaration in Table 1, page 8, 40% of the embryos produced by method 2 developed into calves using MII enucleated oocytes, not telophase oocytes (there is an apparent error in the Declaration);
2. The Declaration provides results from a much narrower method than the method claimed; and

3. There is no disclosure in the specification of using roscovitine arrested donor cells or of using confluent arrested fibroblasts as donors.

In response, Applicants herein cancel claims 25 and 27 without prejudice thereby rendering the rejection moot. Applicants do not acquiesce that any of the Examiner's comments are true or meritorious but rather choose to pursue other claims more clearly describing the invention.

2. Echelhard, U.S. Patent 6,580,017 B1

The Examiner rejects claims 1-18 and 20-38 as anticipated by Echelhard. The Examiner contends that Echelhard teaches methods for producing reconstructed goat oocytes, reconstituted goat embryos, methods for producing transgenic goat embryos, and methods of cloning a goat comprising incubating goat oocytes in telophase II and then further incubating the oocyte in the presence of cytochalasin B, enucleating the activated, telophase II oocyte by aspiration, transferring a cultured goat fetal fibroblast which contains a DNA sequence encoding antithrombin III into the perivitiline space of the enucleated oocyte, fusing the reconstructed oocyte by electrofusion, culturing the reconstituted oocyte to produce a transgenic embryo which is then transferred to a surrogate mother. The fibroblast donor cells were inherently in one of G0, G1, S, G2 or M stages.

Applicants previously explained that Echelhard teaches using ethanol for treating oocytes and that this provides negative results when cloning the fibroblast cells. Applicants indicated that the results presented in Table 2 of Echelhard demonstrate that oocytes treated with ethanol in telophase failed to give valuable embryos and fetuses after transfer and that no embryos, fetus or offspring were found still living or in development. Moreover, no pregnancies were observed with embryos generated by the ethanol enucleation/activation protocol. Hence, Applicants explained that the procedure of Echelhard does not work and is not operable. Even further, we explained that Echelhard does not teach or suggest enucleation of activated oocytes performed precisely when undergoing expulsion of a second polarbody or after the activated oocyte has expelled the second polarbody. Such is the case with the methods of the present invention.

The Examiner replies that while the ethanol treated oocytes of the specific example did not yield live born goats, there is no evidence that if mature oocytes were activated at MII with ethanol that live births would not occur. The Examiner says that the present specification supports that theory. That is, the present specification teaches activating MII oocytes, first polarbody containing, with ethanol and permits them to continue to telophase II (citing page 9, step 1). Hence, the Examiner contends that Echelhard's disclosure of ethanol treatment as an activating agent is enabled.

The Examiner contends that the oocytes of Echelhard are inherently activated since they are in telophase. The Examiner cites to column 14, lines 32-35 as evidence that Echelhard teaches enucleation precisely when the oocyte is undergoing expulsion of the second polarbody. Further, the Examiner cites to column 19, lines 21-25 as evidence that Echelhard teaches enucleation of telophase II oocytes by aspirating the extruded second polarbody. Therefore, the Examiner says that Echelhard does teach both enucleation of activated oocytes precisely when undergoing expulsion of the second polarbody or after the second polarbody had been expelled.

Applicants previously explained that Applicants were first to invent the claimed subject matter as well as submitting the research grant proposal. Applicants reiterate this for the record and the Examiner's remembrance.

At this time, in order to advance prosecution, Applicants herein amend claim 1 to read that the activation of the oocytes is performed by "artificial means" in step a). The term "natural" has been removed from claim 20. This amendment can be found in original claims 4 and 30, and previously presented claim 20. Applicanst respectfully submit that the amended claims are even more clearly patentable over Echelard, as is evidenced by the following explanations. The following paragraphs are relevant quotations from Echelard:

> Oocytes were initially incubated in phosphate buffered saline (PBS, Ca^{2+},/Mg^{2+} free) supplemented with 5% FBS for 15 minutes and cultured in M199 + 10% FBS at 38°C. for approximately three hours until the telophase spindle configuration or the extrusion of the second polarbody was reached. All the oocytes that responded to the sequencial

> culture under differential extra cellular calcium concentration treatment were separated and grouped as Telophase II-Ca^{2+} (Column 19, lines 6 to 14).
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> Thereafter, the oocytes were incubated in 30-50 □l drops of M199 + 10% FBS containing 5 μg/ml of cytochalasin-B for 10-15 minutes at 38°C. Oocytes were enucleated with a 30 micron (OD) glass pipette by aspirating the first polar body and approximately 30% of the adjacent cytoplasm containing the metaphase II or about 10% of the cytoplasm containing the telophase II spindle. After enucleation the oocytes were immediately reconstructed (Column 19, lines 18 to 26).

In reference to the second paragraph of page 4 of the Office Action, it is respectfully brought to the Examiner's attention that Echelard teaches fusing of the reconstructed ***embryo***, not oocyte, by electrofusion (Column 19, lines 48-52) and culturing the reconstitute ***embryo***, not oocyte, to produced the transgenic embryo (Column 21, lines 22-24) and culturing the reconstituted ***embryo***, not oocytes, to produce a transgenic embryo [emphasis added].

Again, Echelard teach "For example, oocytes cultured on serum-starved medium become arrested in metaphase. In addition, arrested oocytes can be induced to enter telophase by serum activation". (See, Column 13, lines 40 to 43). Further, Echelhard teach

> Activation refers to the beginning of embryonic development, e.g., replication and DNA synthesis. Activation can be induced by, for example, electric shock (e.g. in electrofusion), the use of ionophores, ethanol activation, or the oocyte can be obtained during a stage in which it is naturally activated, e.g. an oocyte in telophase. (Column 15, lines 15 to 20)

The Examiner says on page 5, second paragraph of the Office Action that "ethanol was used to activate in vivo matured oocytes that arrested prior to second polar body." However, Echelard describe that:

> In vivo matured oocytes were divided into two groups: oocytes with only one polar body evident (metaphase II stage) and the activated telophase II protocol (oocytes with one polar body and evidence of an extruding second polar body). Oocytes in telophase II were cultured in M199 + 10% FBS for 2 to 4 hours. Oocytes that had activated during this period,

> as evidenced by a first polar body and a partially extruded second polar body, were grouped as culture induced, calcium activated telophase II oocytes (Telophase II-Ca^2+) and enucleated. Oocytes that had not activated were incubated for 5 minutes in PBS containing 7% ethanol prior to enucleation. Metaphase stage oocytes (one polar body) were enucleated with a 25-30 micron glass pipette by aspirating the first polar body and adjacent cytoplasm surrounding the polar body (approximately 30% of the cytoplasm) presumably containing methaphase plate. (Column 18, lines 54 to 68 and on column 19, lines 1 to 4)

Applicants respectfully submit that Echelard discloses the ethanol treatment of telophase II oocytes. Further, Echelard does not disclose the use of ethanol to activate *in vivo* matured oocytes that arrested prior to second polar body formation/expulsion.

On page 5, second paragraph of the office action, the Examiner contends that

> There is no evidence in Echelard that if immature oocytes were activated as MII with ethanol that live births would not have occurred. The present specification supports this later theory. The present specification activates MII oocytes, first polar body containing, with ethanol and permits them to continue to telophase II.

Applicants submit that the matter described or disclosed in the present patent application cannot be used to confirm a supposition of information presumably presented in the prior art, and against Applicants' claims of the same application.

Applicants agree with the Examiner that Table II shows that telophase enucleated oocytes yield a twin pregnancy and the birth of one live born kid, as stated on the middle of the second paragraph of page 5 of the Office Action. However, it is respectfully brought to the Examiner's attention that the live born kid was obtained from Telophase II oocytes (oocytes with one polar body and evidence of an extruding second polar body), as described on column 18, lines 54 to 68 and on column 19, lines 1 to 4 set forth, *supra*, which were then cultured in M199 + 10% FBS for 2 to 4 hours. In clear contrast, in the methods presented herein the activation of the oocytes is followed by the enucleation of the oocytes undergoing or that have already undergone the expulsion of a second polarbody. Again, Applicants agree with the Examiner that a telophase oocyte is inherently activated, and hence is in the process of extruding its second polar body.

However, this inherent activation of the telophase oocyte differs from the artificial activation of the oocytes in step a) of independent Claims 1 as presently amended (and claim 20). Further, claim 10 is herein amended to provide consistent language by deleting the expression "or natural" in the step a).

New claims 39 to 42 are herein added. Claims 39 and 40 include the steps of claims 1 and 20, respectively, to which an additional step reciting culturing the activated oocytes to allow the oocytes undergoing the expulsion of a second polar body or expelling the second polar body (Tel-II), has been added. The step of culturing the oocytes after activation, and before the enucleation step while the oocytes are undergoing the expulsion of a second polar body or expelling the second polarbody (Tel-II) is not described in the prior art. Support for this amendment can be found on page 9, lines 8 to 10, and on page 10, lines 10 to 12 of the specification. New claims 41 and 42 include respectively the steps of claims 1 and 20, but further specifically recite that the species is bovine. Support for this amendment can be found in Examples 1 to 7 provided in the specifications.

The present claims recite in sequence that an oocyte is activated, then enucleated at the stage when the expulsion of a second polar body is undergoing or when the second polar body has been recently expelled, and in which is transferred a nucleus from mammalian germinal or somatic cells to obtain a reconstructed mammalian oocyte. Echelard simply does not teach or suggest this. Applicants submit that the claims are both new and inventive in light of Echelard.

Fees

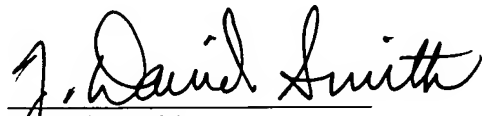
No additional fees are believed to be necessitated by the instant Response. However, should this understanding be erroneous, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or to credit any overpayments.

CONCLUSION

Applicants respectfully request entry of the foregoing Amendments and Remarks into the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited. Should a discussion be helpful in resolving any outstanding issues, the Examiner is invited to telephone the undersigned at (201) 487-5800.

Respectfully submitted,

KLAUBER & JACKSON



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